

## Ask the Experts: Issues Related to the Management of Postoperative Pain

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## Learning Objectives

At the conclusion of this activity, participants should be able to

- Address current issues related to multimodal therapy for postoperative pain management
- Outline factors to consider when evaluating local anesthetics for postoperative pain management

## Mission Impossible or Not?

### Your Mission:

Determine the best perioperative multimodal pain regimen for a new order set for total knee arthroplasty



## Audience Poll



You have to make your decision on one of the multimodal mission choices below.

| A   | B  | C   |
|---|--|---|
| <ul style="list-style-type: none"><li>• Opioid</li><li>• NSAID or acetaminophen</li><li>• Pregabalin</li><li>• Local anesthetic nerve block</li></ul> | <ul style="list-style-type: none"><li>• Opioid</li><li>• NSAID or acetaminophen</li><li>• Local anesthetic nerve block</li></ul> | <ul style="list-style-type: none"><li>• Opioid</li><li>• NSAID or acetaminophen</li></ul> |

NSAID = nonsteroidal anti-inflammatory drug, LA = local anesthetic

### Our Quest Begins:

What is the best multimodal regimen?

- Ovid Medline search from 1996-2013
- Search terms
  - Multimodal and pain management (420)  
Limit to randomized, controlled trials (68)
  - Multimodal and analgesia (695)  
Limit to randomized, controlled trials (203)
  - Randomized, controlled trials for arthroplasty total knee with multimodal pain management or multimodal analgesia (40)

### When should long-acting opioids be used?

- Food and Drug Administration (FDA): updated label to state long-acting and extended release opioids are indicated in selected pain management situations<sup>1</sup>
  - Pain severe enough to require daily around-the-clock administration
  - Alternative treatment options are inadequate
- American Academy of Orthopaedic Surgeons<sup>2</sup>
  - Preop: Long-acting oxycodone 10 mg orally for patients ≥ 75 years and 20 mg orally for patients < 75 years
  - Postop: Long-acting oxycodone 10 mg or 20 mg orally (depending on preop dose) every 12 hours for 24 hours postop

<sup>1</sup>U.S. Food and Drug Administration. News release. Sept 10, 2013. URL in ref list.

<sup>2</sup>Dalury DF et al. *J Bone Joint Surg Am.* 2011; 93:1938-43.

## Long-Acting Morphine Study

- Randomized, double-blind study of 200 patients with standard postop pain management and one of the following
  - Treatment group: Long-acting morphine 30 mg orally twice daily for 3 days
  - Control group: Placebo orally twice daily for 3 days
- Results
  - Change in pain scores did not reach clinical significance for either group
  - No statistical difference between groups for general activity and walking 72 hours after surgery
  - Opioid group
    - Increase opioid use ( $P < 0.0001$ )
    - Vomiting ( $P = 0.0148$ )
    - Oversedation ( $P = 0.08$ )

Musclow SL et al. *Pain Res Manag.* 2012; 17:83-8.

## IV Opioid PCA vs. Long-acting Oxycodone

- TKA or THA cohorts matched for demographic characteristics, surgical procedure, surgeon, and anesthesia
  - 62 patients: IV opioid patient-controlled analgesia (PCA)
  - 62 patients: long-acting oxycodone 20 mg orally twice daily for 3 days with oxycodone 5-20 mg po q 3 hours as needed
- Results
  - Both groups: similar pain ratings all 3 days
  - Oxycodone group: less opioid compared with IV PCA in first 24 hr postop ( $37.8 \text{ mg} \pm 23.45$  vs.  $59.4 \text{ mg} \pm 37.0$ ,  $P < 0.001$ )
  - Oxycodone group: interference with walking on day 1 ( $P = 0.24$ ), deep breathing on day 2 ( $P = 0.11$ )
  - Statistical difference in patient satisfaction with pain management only on day 3 with oxycodone

TKA = total knee arthroplasty  
THA = total hip arthroplasty

Illgen RL et al. *J Arthroplasty.* 2006; 21:814-20.

## Chronic Opioid User

- TKA opioid and nonopioid cohorts matched for surgical center, procedure, age, sex, body mass index, preop diagnosis and insurance
  - 49 patients in chronic opioid group
  - 49 patients in nonopioid group
- Results

| Outcome                                 | Chronic Opioid User | Non-opioid User | P Value |
|---|---------------------|-----------------|---------|
| # days to discharge                     | 4.3                 | 3.4             | 0.013   |
| Surgical revision for pain or stiffness | 8                   | 0               | <0.001  |
| Referral to pain specialist             | 10                  | 1               | <0.001  |

Zywiel MG et al. *J Bone Joint Surg Am.* 2011; 93:1988-93.

## Order Set Tips for Postoperative Opioids in Adult Patients



- Create selection buttons to force prescriber to acknowledge the patient's age
  - Age < 65 years
  - Age ≥ 65 years
- Create separate headers for long-acting and short-acting opioids to improve prescribing safety
- Clarify opioid naïve vs. tolerant for doses
- Identify drugs and doses that are appropriate for patients with renal impairment
- Provide instructions for starting long-acting oral opioids when patient on IV PCA

## Example: Postoperative Long-Acting Opioids University of Minnesota Medical Center

- Long-acting oxycodone dose in elderly 10 mg orally twice daily
- Long-acting oxycodone for opioid-tolerant patients only

Moderate to severe pain - Oral opioids (Long Acting - ONLY for OPIOID TOLERANT patient) select one  
☐ Long acting oxycodone for > 65 years old with low urine output or low GFR  
☐ Long acting oxycodone (NOT for elderly patients with poor renal function)

EPIC Order Set Instruction: patient must be opioid-tolerant taking an equivalent of 30 mg oral morphine per day

## Example: Postoperative Pain Orders for Elderly University of Minnesota Medical Center

Moderate to severe pain - Oral opioids (short acting - immediate release) select one

Pain Meds for > 65 years old with low urine output or low GFR

☐ oxycodone (ROXICODONE) immediate release tablet

5 mg, Oral, EVERY 3 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing, Post-procedure

☐ oxycodone-acetaminophen (PERCOCET) 5-325 MG per tablet

1 tablet, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing, Post-procedure

☐ hydrocodone-acetaminophen (NORCO) 5-325 MG per tablet

1 tablet, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing, Post-procedure

☐ hydrocodone-acetaminophen (LORTAB) solution 7.5-325 mg/15 mL

10 mL, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing, Post-procedure

☐ hydromorphone (DILAUDID) tablet

1-2 mg, Oral, EVERY 3 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing, Post-procedure

See page 10 for enlarged view

See page 10 for enlarged view

## Acetaminophen

- Central mechanisms
  - Inhibits cyclooxygenase in locations where ambient peroxidase is low (i.e., brain)
  - Reinforces descending serotonergic inhibitory pain pathway
  - Cannabinoid receptor agonist
- Absorption after 1000 mg dose
  - Oral Tmax 45 minutes, Cmax 15.1 mcg/mL
  - Intravenous Tmax 25 minutes, Cmax 28.4 mcg/mL
- Maximum analgesic and antipyretic activity occurs 1-2 hours after peak plasma levels

Lachiewicz PF. *Orthopedics*. 2013; 36(suppl 2):15-9.

## Acetaminophen Paradox

- Intravenous vs. oral preoperatively
  - Evidence does not support one route over another
  - Cost is the driver toward oral
- Maximum dose limit
  - Literature recommends  $\leq 3000$  mg per day for chronic use<sup>1</sup>
  - FDA still allows 4000 mg per day maximum
- Combined with opioids
  - Low acetaminophen dose (325 mg per dosage unit) inadequate for pain relief
  - Commonly used for postoperative pain management

<sup>1</sup>Watkins PB et al. *Reg Anesth Pain Med*. 2011; 36:417-9.

## Example: Acetaminophen Route Interchange University of Minnesota Medical Center

- For conversion from intravenous to oral, patient must be receiving other medications orally or through a gastric tube that are intended for systemic therapeutic purpose.
- Pharmacist can substitute oral acetaminophen without discussion with the medical team as long as patient able to take oral medications.

## IV Acetaminophen Use: Examine Your Evidence

- Medication-use evaluation
  - Indication
  - Patient oral status
  - Prescriber trends
- Cost assessment
  - Comparison based on use outside of justified indications

Which of the following is a valid concern with postoperative use of NSAIDs for total knee arthroplasty?  
Select all that apply.



- a. Impaired tissue healing
- b. Non-union of joint
- c. Cardiovascular event in patient 6 months post myocardial infarction
- d. Use in a patient 60 years of age

## Tissue and Bone Healing

- Non-union studies are cohort and case-controlled due to the low number of patients reported
  - Meta-analysis of spine studies found no statistically significant difference with NSAIDs vs. no NSAIDs<sup>1</sup>
  - Non-union of bone not a complication with total joint arthroplasty
- Soft tissue healing relies on platelet-derived growth factors so NSAID use is not detrimental to healing
- Studies needed in humans on NSAID inhibition of soft tissue to bone healing
- Retrospective studies show delayed healing of bone fractures with NSAIDs<sup>2</sup>

<sup>1</sup>Dodwell ER et al. *Calcif Tissue Int*. 2010; 87:193-202.

<sup>2</sup>Chen MR et al. *Knee Surg Sports Traumatol Arthrosc*. 2013; 21:540-9.

## Cardiovascular Risks

- No well-tolerated window for NSAID use after MI
- Large Danish cohort study of 99,187 patients post MI

| Risk of Death Associated with NSAIDs after MI |             |                    |
|---|-------------|--------------------|
| Year  | # of Events | Hazard Ratio       |
| 1   | 1086        | 1.59 [1.49-1.69]   |
| 2   | 712         | 1.84 [1.70 – 1.69] |
| 3   | 546         | 1.81 [1.66 – 1.99] |
| 4   | 468         | 1.83 [.66 – 2.01]  |
| 5   | 377         | 1.73 [1.56 – 1.93] |
| >5  | 963         | 1.63 [1.52 – 1.74] |

MI = myocardial infarction  
 Olsen AM et al. *Curr Opin Cardiol.* 2013; 28:683-8.  
 Olsen AM et al. *Circulation.* 2012; 126:1955-63.

## Is naproxen safe post MI?

- FDA Advisory Committee review of post marketing cardiovascular safety from 2006-2013 (1/10/2014)
- Majority of data from observational studies or meta-analysis
- Results
  - No evidence of statistically significant increased risk of MI or stroke during OTC or prescription use of naproxen
  - Selected data suggest some interaction between naproxen and the antiplatelet activity of aspirin, if dosed prior to or concomitantly with aspirin
- Review of thromboembolic risk with non-aspirin NSAIDs will occur in February 2014
- Recommendations for changes in naproxen labeling will be reviewed by a cardiology advisory panel

U.S. Food and Drug Administration. FDA briefing document. January 28, 2014. URL in ref list.

## Gabapentin

- Design flaws common with studies
- Randomized, double-blind study in total knee arthroplasty
  - Preop for both groups: 1000 mg acetaminophen oral and 15 mg ketorolac oral
  - Treatment group: 52 subjects gabapentin 600 mg oral preop and 200 mg oral every 8 hr x 2 days postop along with morphine intravenous patient controlled analgesia
  - Control group: 49 subjects placebo along with morphine intravenous patient controlled analgesia
- Results
  - Morphine consumption primary outcome
    - 66.3 mg gabapentin group vs. 72.5 mg placebo (P=0.59)
  - No difference in pain score
- Limitations: Postop gabapentin dose low and primary-end point not a definitive outcome

Paul JE et al. *Can J Anaesth.* 2013; 60:423-31.

## Pregabalin

- Randomized, double-blind study in total knee arthroplasty
  - Both groups: celecoxib 400 mg preop and epidural with fentanyl and bupivacaine postop
  - Treatment group: 113 patients received oral pregabalin 300 mg preop, 150 mg twice daily days 1-10, 75 mg twice daily days 11-12, 50 mg twice daily days 13-14
  - Control group: 115 patients received placebo
- Results
  - Pregabalin group used less epidural opioid infusion than placebo (5.77±1.31 mL/hr vs. 6.40±1.26 mL/hr, P=0.003)
  - Greater flexion over 30 days with pregabalin group
  - Less neuropathic pain, allodynia, and hyperalgesia at 3 and 6 months postop with pregabalin group

Buvanendran A et al. *Anesth Analg.* 2010; 110:199-207.

## Example of Preoperative Analgesia Protocol for TKA

| MEDICATION   | DOSE                 | CAUTION   |
|--|----------------------|---|
| Acetaminophen  | 1000 mg oral or IV   | Avoid in patients with liver disease                                    |
| Celecoxib  | 200 mg – 400 mg oral | Avoid in patients with renal disease or sulfur allergy                  |
| Naproxen   | 500 mg oral          | Use if patient has sulfur allergy; avoid in patients with renal disease |
| Pregabalin   | 75 mg oral           | Avoid in patients at risk for postoperative delirium                    |
| Protocol: Give medications 1 hour before surgery with sips of water. |                      |   |

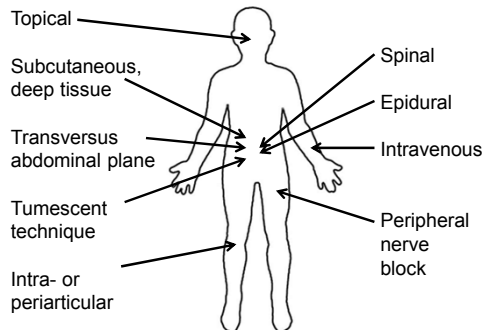
Parvizi J et al. *Orthopedics.* 2013; 36(suppl 2):7-14.

## Your Mission Continues...

The surgeon requests liposome bupivacaine for total knee arthroplasty

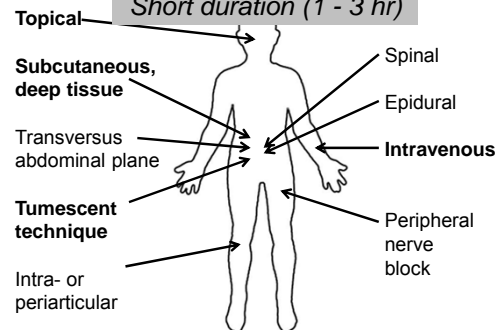


### Perioperative Routes of Administration of Local Anesthetics



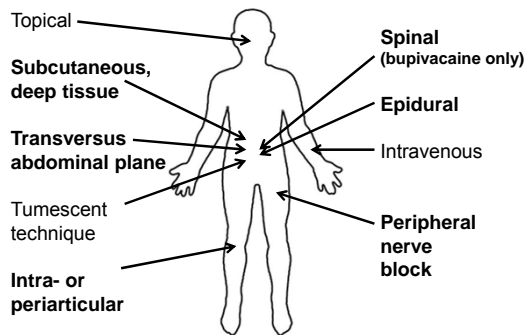
### Perioperative Lidocaine Administration

**Lidocaine**  
Fast onset,  
Short duration (1 - 3 hr)



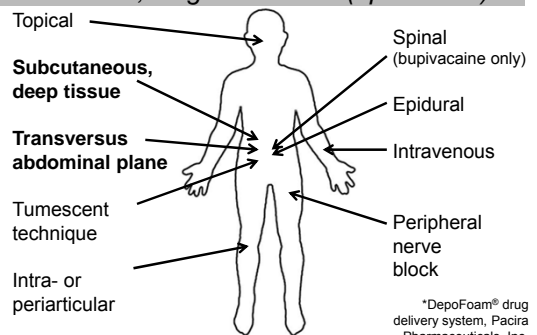
### Bupivacaine and Ropivacaine

Slow onset, longer duration (2 - 8 hr)



### Liposome Bupivacaine\*

Fast onset, longest duration (up to 72 hr)



\*DepoFoam® drug delivery system, Pacira Pharmaceuticals, Inc.

### Continuous Wound Catheters

- 32 randomized controlled trials (RCTs)
  - Obstetrical and gynecologic surgery
  - Major abdominal surgery
  - Inguinal herniorrhaphy
  - Cardiothoracic surgery
  - No orthopedic surgery
- Patients with continuous wound catheters
  - No significant reduction in pain at rest or with activity, except OB-gyne surgery
  - No significant reduction in opioid consumption except for first 24 hr in OB-gyne surgery
  - Magnitude of these effects was small

Gupta A et al. *Acta Anaesthesiol Scand*. 2011; 55:785-96.

### Local Infiltration Analgesia (LIA): Orthopedic Surgery

- 10 reports (N = 893)
  - 8 RCTs, two case series
  - Hip resurfacing arthroplasty, total hip replacement, total knee replacement
- Results
  - 8 reports → LIA was an effective analgesic
  - 2 reports → no benefit when LIA was added to a multimodal analgesic regimen
  - LIA efficacy questioned in total hip replacement

McCarthy D et al. *Anesthesiol Res Pract*. 2012; 2012:709531.

## Additives

- **Epinephrine<sup>1</sup>**
  - Slows systemic absorption, lowering peak plasma concentration of local anesthetic
  - Prolongs duration of lidocaine and mepivacaine
  - High epinephrine concentration (e.g., > 5 mcg/mL) reduces bleeding
- **Ketorolac<sup>2</sup>**
  - Analgesic effects when given locally or systemically
- **Clonidine<sup>3</sup>**
  - Prolongs duration of peripheral nerve block by about 2 hr, but adverse effects can be problematic

<sup>1</sup>Rosenberg PH et al. *Reg Anesth Pain Med*. 2004; 29:564-75.

<sup>2</sup>Romsing J et al. *Acta Anaesthesiol Scand*. 2000; 44:672-83.

<sup>3</sup>Popping DM et al. *Anesthesiology*; 2009; 111:406-15.

## Periarticular Injection Additives

- Assess pain severity, range of motion, inpatient walking distance, and Knee Society Score (KSS) in 160 adults undergoing total knee arthroplasty
- Randomized to
  - Ropivacaine + epinephrine + ketorolac + clonidine (group A)
  - Ropivacaine + epinephrine + ketorolac (group B)
  - Ropivacaine + epinephrine + clonidine (group C)
  - Ropivacaine + epinephrine (group D, control group)
- Results
  - Significantly lower pain scores in groups A and B vs. group D
  - No significant differences between groups for range of motion, inpatient walking distance, functional KSS, or mean postop opioid consumption

Kelley TC et al. *J Arthroplasty*. 2013; 28:1274-7.

## Additives: Morphine

- Systematic review, intra-articular morphine, arthroscopic knee surgery
- 45 studies identified but only 19 studies suitable for meta-analysis
  - Reduction in pain intensity (12 - 17 mm) in morphine group vs. placebo in early (0 - 2 hr), intermediate (2 - 6 hr) and late (6 - 24 hr) phases
  - Six studies found decreased postop opioid consumption; six studies found no difference
  - No clear dose-response effect
  - Systemic effect could not be ruled out
- Conclusion: "definite but mild analgesic effect"

Gupta A et al. *Anesth Analg*. 2001; 93:761-70.

## Liposome Bupivacaine (LB): Pooled Results, Phase 2 & 3 Trials (N = 10)

- Cumulative pain scores
  - 16/17 treatment arms favored LB through 24 hr
  - 5/17 treatment arms favored LB through 72 hr
- Time to first use of rescue opioid
  - Longer with LB (9.3 hr) vs. bupivacaine hydrochloride (bupivacaine) (6.4 hr, P = 0.013) and placebo (3.6 hr, P < 0.0001)
- Proportion of patients avoiding opioid rescue
  - 1 study favored LB; no difference in 8 studies
- Total postop opioid consumption
  - 4 studies favored LB at 24 hr; 2 studies favored LB at 72 hr
- Patient satisfaction
  - 1/6 studies favored LB at 24 hr and 72 hr

Bergese SD et al. *J Pain Res*. 2012; 5:107-16.

## Liposome Bupivacaine: Phase 4 Trials

Study design: Multicenter, open-label, sequential groups  
Study groups: IV PCA vs. multimodal analgesia (liposome bupivacaine, scheduled NSAID and APAP for 72 hr, opioid rescue)  
Primary outcomes: total postop opioid consumption, length of stay, and hospital costs

|  | Ileostomy Reversal<br>(Marcet et al. <i>J Pain Res</i> . 2013; 6:549-55) | Laparoscopic Colectomy<br>(Candiotti et al. <i>Curr Ther Res</i> . 2014; 76:1-6) |
|--|--|--|
| N (PCA, multimodal)                    | 27 (11, 16)  | 82 (56, 26)  |
| Total postop opioid consumption (mean) | 112 mg PCA vs. 20 mg multimodal (P<0.01)                                 | 96 mg PCA vs. 32 mg multimodal (P<0.0001)  |
| Length of stay (median)                | 5.1 days PCA vs. 3.0 days multimodal (P<0.001)                           | 4.0 days PCA vs. 3.0 days multimodal (P=0.0019)                                  |
| Hospital costs (geometric mean)        | \$9,282 PCA vs. \$6,484 multimodal (P=0.01)                              | \$13,018 PCA vs. \$11,234 multimodal (P=NS)                                      |

## Liposome Bupivacaine vs. Continuous Wound Catheter

- Retrospective, single surgeon, robotic-assisted and laparoscopic urologic surgery
  - 54 consecutive patients received ropivacaine infusion; next 54 patients received liposome bupivacaine
- Primary endpoint: postop opioid consumption
- Liposome bupivacaine group had
  - Lower postop opioid consumption (23.8 vs. 65.9 mg; P<0.0001)
  - Longer time to first opioid use (186 vs. 64 min, P=0.043)
  - No difference in length of stay (1.6 vs. 1.8 days; P=0.64)

Walker PW et al. *J Endourol*. 2013; 27(Suppl):A41-2. Abstract MP2B-24.

### Compatibility of Liposome Bupivacaine with

- Bupivacaine HCl
  - LB:bupi HCl ratio  $\leq 1:12 \rightarrow$  excessive release of free bupivacaine
  - LB:bupi HCl ratio  $\geq 2:1 \rightarrow \leq 5\%$  release of free bupivacaine
  - "Co-administration of both drug forms will increase overall exposure to bupivacaine."
- Lidocaine, ropivacaine, mepivacaine
  - If given 1, 5, or 10 min before LB, rapid release of free bupivacaine
  - If given 20 or 40 min before LB, free bupivacaine does not increase
- Epinephrine
  - Minor physicochemical interaction
- Morphine 10 mg and ketorolac 30 mg
  - Minimal increase in free bupivacaine levels

Kharitonov V. *Postgrad Med.* 2014; 126:129-38.

### Exparel (bupivacaine liposome injectable suspension) prescribing information. Pacira Pharmaceuticals, Inc.; 2011 Oct.

- "Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl, when injected immediately before EXPAREL, may impact the pharmacokinetic and/or physiochemical properties of the drugs when the milligram dose of bupivacaine HCl solution exceeds 50% of the EXPAREL dose. EXPAREL contains bupivacaine; therefore, coadministration of both drugs will increase the overall exposure to bupivacaine.
- EXPAREL should not be admixed with other drugs prior to administration.

Kharitonov V. *Postgrad Med.* 2014; 126:129-38.

### Transversus Abdominis Plane (TAP) Block

- Technique
  - Ultrasound-guided
  - Laparoscopic assisted
  - Direct visualization
- Provides analgesia for surgery involving lower abdominal wall
  - Bowel surgery, appendectomy, cesarean delivery, hysterectomy, prostatectomy, laparoscopic cholecystectomy
- Optimal surgical procedures, dosing, technique and timing are not clear

Young MJ et al. *Anesthesiol Res Pract.* 2012; 2012:731645.  
 Abdallah FW et al. *Br J Anaesth.* 2012; 109:679-87.  
 Siddiqui MR et al. *J Clin Anesth.* 2011; 23:7-14.

### TAP Block after Laparoscopic Surgery

- Systematic review
  - 10 RCTs, 633 subjects
  - TAP block (ultrasound-guided) vs. placebo (or no treatment)
- Primary outcomes
  - Early (0-4 hr) and late (24 hr) postop pain at rest and on movement
  - Postop opioid consumption (up to 24 hr)
- Results
  - TAP block reduced early and late pain at rest and postop opioid consumption; no improvement in early and late pain with movement or postop nausea/vomiting
  - Preop administration more effective than postop
  - Association between total dose and opioid consumption

De Oliveira GS Jr et al. *Anesth Analg.* 2014; 118:454-63.

### Peripheral Nerve Blocks and IV Lidocaine

- Systematic review evaluated preventive analgesia\* by local anesthetics
  - 89 peripheral nerve block studies
    - TKA, THA, anterior cruciate ligament (ACL) reconstruction, arthroscopic knee and shoulder surgery, foot and ankle surgery, open shoulder surgery, hand/upper limb surgery, TAP block for various abdominal and bowel surgeries
  - 16 IV lidocaine studies
- Primary outcome
  - Postoperative pain and/or opioid consumption

\* Defined as a reduction of postoperative pain that persists for more than 5.5 half-lives (8 hr for lidocaine and 12-16 hr for bupivacaine and ropivacaine)

Barrevelde A et al. *Anesth Analg.* 2013; 116:1141-61.

### Results

- Peripheral nerve blocks
  - Provide better analgesia than placebo, PCA, and intra-articular infusions
  - Some effects attributed to systemic distribution
  - Total dose appears to be more important than volume and concentration
  - Timing of block (before or after incision) does not appear to affect efficacy
- IV lidocaine
  - Provided better analgesia than placebo (0.9% sodium chloride) in 13/16 studies

Barrevelde A et al. *Anesth Analg.* 2013; 116:1141-61.

## Liposome Bupivacaine and Total Knee Arthroplasty: Wound Infiltration

- Phase 2, dose-ranging study<sup>1</sup>
  - LB 133, 266, 399, and 532 mg vs. bupivacaine 150 mg + epinephrine
  - LB 532 mg provided better analgesia than bupivacaine + epinephrine
- Emerging reports of experiences in individual surgeon practices<sup>2</sup>

<sup>1</sup>Bramlett K et al. *Knee*. 2012; 19:530-6.

<sup>2</sup>Barrington JW et al. *Am J Orthop*. 2013; 42(suppl):S1-S15.

## Maximum Recommended Dose and Plasma Concentration

- Although not necessarily evidence-based, maximum dose highlights "dose" as a risk factor for systemic toxicity
- "...because drug concentrations in various regions of heart and brain tissue differ quite markedly, the deterministic notion of a "toxic" or "lethal" blood or tissue concentration of local anesthetic appears invalid even with standardized conditions. Others have noted that blood concentrations of local anesthetics in dogs that survived a particular dose were not significantly different from pre-mortem blood concentrations in those that died."<sup>1,2</sup>

<sup>1</sup>Feldman HS et al. *Anesth Analg*. 1989; 69:794-801.

<sup>2</sup>Copeland SE et al. *Anesth Analg*. 2008; 106:1440-9.

## Local Anesthetic Systemic Toxicity (LAST)

- More than one third of reports involved patients with underlying cardiac, neurologic, renal, hepatic, pulmonary, or metabolic disease
- Treatment is different from other cardiac arrest scenarios
  - Airway management, seizure suppression (avoid propofol)
  - Avoid vasopressin, calcium channel blockers, beta-blockers, local anesthetics
  - Reduce epinephrine doses to < 1 mcg/kg
  - Lipid emulsion (20%)
    - 1.5 mL/kg (lean body mass) over 1 min, then 0.25 mL/kg/min infusion
    - Repeat bolus once or twice for persistent cardiovascular collapse
    - Double infusion rate if blood pressure remains low
    - Continue infusion for at least 10 min after circulation stabilizes
    - Upper limit: 10 mL/kg over first 30 min

Neal JM et al. *Reg Anesth Pain Med* 2010; 35:152-61.

Rosenberg PH et al. *Reg Anesth Pain Med*. 2004; 29:564-75.

Weinberg G. LipidRescue Resuscitation for drug toxicity. URL in ref list.

## Example: Colorectal Surgery

- Open
- Minimally-invasive
  - Laparoscopic
  - Robotic-assisted



## Laparoscopic Colorectal Surgery

- Assessed efficacy of SC bupivacaine +/- IP lidocaine in reducing postoperative pain
- Case-controlled, sequential cohorts\*
  1. No local anesthetic (control group) (N = 61)
  2. SC bupivacaine in all ports and wound (N = 67)
  3. SC bupivacaine + IP lidocaine under diaphragm and within peritoneal cavity (N = 44)
- Enhanced recovery pathway
  - PCA, avoid drains and tubes, early feeding and mobilization
- Results
  - No difference between groups in VAS
  - No difference between groups in amount of postoperative opioid

\*After surgeon performed > 600 laparoscopic colorectal procedures

SC = subcutaneous, IP = intraperitoneal, PCA = patient-controlled analgesia, VAS = visual analog score

Stuhldreher JM et al. *Surg Endosc*. 2012 ;26:1617-23.

## Enhances Recovery After Surgery (ERAS®)

- Comprehensive for entire surgical process, particularly key factors that prevent hospital discharge
  - Need for parenteral analgesics
  - Need for IV fluids secondary to gut dysfunction
  - Lack of mobility
- ERAS for colorectal surgery<sup>1</sup>
  - Pre-, intra- and post-operative protocol with about 20 care elements
    - Examples of care elements: preoperative patient education, fluid management, no drains, early oral nutrition, epidural + acetaminophen + NSAID analgesia
  - 137 patients in ERAS program compared with historical cohort (N=99)
  - Significantly reduced<sup>2</sup>
    - Length of stay (6 vs. 8.4 days, P<0.001)
    - Readmissions (8.8% vs. 20.2%, P=0.012)
    - Hospital costs (by 15%)

<sup>1</sup>Enhances Recovery After Surgery (ERAS) Society. ERAS protocol (EP). URL in ref list.

<sup>2</sup>Miller T et al. Presented at ASA Annual Meeting; October 15, 2013. Abstract A4293.



## Back to Request from Surgeon for Liposome Bupivacaine . . .

- Evaluate current state
  - Use of multimodal analgesia
  - Protocol and order sets
  - Enhanced recovery pathway
- Expected outcome(s)
  - Pain intensity, HCAHPS patient satisfaction scores, opioid use, adverse effects, length of stay, etc.
- Limited trial, attention to safety
- Medication-use evaluation

HCAHPS = Hospital Consumer Assessment of Healthcare Providers and Systems

## Another Long-acting Bupivacaine in Development . . .

- Saber® delivery system
  - 15 clinical trials, various surgical procedures
  - Up to 72 hr
- Prescription Drug User Fee Act (PDUFA) date of February 12, 2014

Durect Corporation. [http://www.durect.com/wt/durect/page\\_name/postop](http://www.durect.com/wt/durect/page_name/postop) (accessed 2014 Jan 27).

## Mission Impossible or Not?

### Your Mission:

Determine the best perioperative multimodal pain regimen for a new order set for total knee arthroplasty



## Audience Poll



You have to make your decision on one of the multimodal mission choices below.

| A   | B  | C   |
|---|--|---|
| <ul style="list-style-type: none"><li>• Opioid</li><li>• NSAID or acetaminophen</li><li>• Pregabalin</li><li>• Local anesthetic nerve block</li></ul> | <ul style="list-style-type: none"><li>• Opioid</li><li>• NSAID or acetaminophen</li><li>• Local anesthetic nerve block</li></ul> | <ul style="list-style-type: none"><li>• Opioid</li><li>• NSAID or acetaminophen</li></ul> |

NSAID = nonsteroidal anti-inflammatory drug, LA = local anesthetic

## Conclusion

- Know your institution
  - Organizational structure, resources, type of services and specialties
- Work as a interprofessional team
- Formulate a plan, implement, and evaluate
  - Data driven
  - Safety

## Example: Postoperative Long-Acting Opioids University of Minnesota Medical Center

- Long-acting oxycodone dose in elderly 10 mg orally twice daily
- Long-acting oxydodone for opioid-tolerant patients only

▼ Moderate to severe pain - Oral opioids (Long Acting - ONLY for OPIOID TOLERANT patient) select one

- ☐ Long acting oxyCODONE for > 65 years old with low urine output or low GFR
- ☐ Long acting oxyCODONE (NOT for elderly patients with poor renal function)

EPIC Order Set Instruction: patient must be opioid-tolerant taking an equivalent of 30 mg oral morphine per day

## Example: Postoperative Pain Orders for Elderly University of Minnesota Medical Center

▼ Moderate to severe pain - Oral opioids (short acting - immediate release) select one

☒ Pain Meds for > 65 years old with low urine output or low GFR

☐ oxyCODONE (ROXICODONE) immediate release tablet

5 mg, Oral, EVERY 3 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing., Post-procedure

☐ oxyCODONE-acetaminophen (PERCOCET) 5-325 MG per tablet

1 tablet, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing., Post-procedure

☐ HYDROcodone-acetaminophen (NORCO) 5-325 MG per tablet

1 tablet, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing., Post-procedure

☐ HYDROcodone-acetaminophen (LORTAB) solution 7.5-325 mg/15 mL

10 mL, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing., Post-procedure

☐ HYDROmorphine (DILAUDID) tablet

1-2 mg, Oral, EVERY 3 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing., Post-procedure